Microwave irradiation assisted synthesis of cyclohexenes via one pot reaction techniques

Shaaban. K. Mohamed, Antar A. Abdelhamid, A.M. Maharramov, A. N Khalilov, F.N. Nagiyev, and M. A. Allahverdiyev

Department of Organic Chemistry, Baku State University, Baku, Azerbaijan
Chemistry and Environmental Division, Manchester Metropolitan University, Manchester, UK.

ABSTRACT

Microwave irradiation of three components of primary amino alcohols, acetylacetone, and aromatic aldehydes afforded the formation of amino-cyclohexene derivatives in a very good yield (average 85%). The products have been characterized by $^1$HNMR, $^{13}$CNMR, IR and mass spectra.

Keywords: Microwave irradiation, three-components reaction, one pot reactions, amino alcohols, aldehydes, β-Diketone, cyclohexenes.

INTRODUCTION

Microwave irradiation consider as a new and a facile method for the synthesis and preparation of the cyclohexene ring. The cyclohexene ring is not a very common structural element in medicinal chemistry, which means that few drugs have a substituted cyclohexene ring as core structure. One of the reasons is that it is not easy to synthesize chiral substituted cyclohexenes in high enantiomeric excess and in bulk quantities. In contrast, the cyclohexene ring often occurs in natural compounds such assteroids, vitamin A, taxol, as components of ethereal oils such as limonene, morphines, (−)-mesembrine and other like the syntheses of (−)-tubifoline and (−)-strychine. In the first examples, the cyclohexene ring is derived from isoprene chemistry while in the last example; the cyclohexene ring originates from l-tyrosine [1-8].

2-Cyclohexene-1-one (CHX, CAS 930-68-7) occurs as a natural ingredient in certain fruits such as breadfruit, babaco and chayote [9,10] and has also many use as an antifungal agent. Some of cyclohexene derivatives like as cyclohexyl mercaptan used as starting material for manufacture of biologically active compounds such as inhibitors of prostaglandin and leukotriene; canine COX-2 inhibitors; hosphodiesterase inhibitors [11,12]. The mesomorphic derivatives of cyclohexylbenzene and trans, transdicyclohexylbenzene are very useful in liquid crystalline mixtures because they have low melting points and a low viscosity[ 13-19].

Since the first cyclohexene has been synthesized via the well know Diels-Alder reaction on 1928 [20], it stimulated the interest of chemists to developed variety of synthetic methods for cyclohexenes and their derivatives. The vast majority of these methods have been based on the use of different types of catalysts and reagents such as indium complex [21], 2-[bis(3,5-bis-trifluoromethylphenyl)triethylsiloxyethyl]pyrroolidine salt in water [22], cationic
silicon Lewis acids [23], a mixture of AlCl₃ and THF [24], organocerium reagents [25], iridium-catalyzed borylation of cyclic alkenes [26], iron-catalyzed cross-coupling of primary alkyl Grignard reagents [27], trialkylphosphines and alkyl halides [28, 29], combined catalysts of AuCl₃/AgSbF₆ or AuCl₃/AgOTf [30], tributylphosphine and Pd(Ph₃P)₄ [31], rhodium-catalyzed cycloisomerization of acyclic enynes [32], GaCl₃-catalyzed skeletal reorganization of enynes [33] and Ru-catalyzed decarbonylative cyclization [34]. Recently, Sargsyan et al [35, 36] has reported the synthesis of similar structures of aminocyclohexenes from imino and amino alcohols respectively at room temperature for 2-3 days with relatively low yield.

As the whole world now is emphasizing the significance of green chemistry, so, in this study we are reporting a new methodology in synthesis of amino cyclohexene derivatives under free catalyst condition and microwave technique via one pot of three component reactions. This friendly environmentally technique is an extension to our belief that “the best catalyst is no catalyst”[37,38]. The significance of our protocol is to lower the toxicity of use of catalysts and avoiding multistep reactions which mostly accompanied with waste of chemicals and side products in addition to the waste of energy. Further to our previous work of synthesis of some alicyclic compounds by the three-component or Multicomponent component condensation and studying the relation of their functional activity with chemical structure [39-44], we are reporting in this study the significant use of microwave irradiation in synthesis of cyclohexene derivatives and the effect of microwave on developing of their yield comparing to the conventional heat results. The synthesis has been carried out via one pot reaction of aminoalcohols with aromatic aldehydes and acetylacetone to lead ultimately the formation of 5-N-(2-hydroxyalkyl)amino-2,4-diacetyl-1,4-cyclohexen-1-ol 3a-d (Scheme 1).

![Scheme 1](image)

**EXPERIMENTAL SECTION**

Mp’s were determined using open glass capillaries on a Gallenkamp digital melting point apparatus and are uncorrected. The reactions have been carried out in a domestic microwave oven at power of 750w. The IR spectra were recorded with Varian 3600 FT-IR instrument using potassium bromide pellets. The 1H-NMR (300 MHz) and 13C-NMR (75 MHz) spectra were measured in DMSO-d6 using a Fimm Bruker AV300 system with TMS as an internal standard. Chemical shifts are expressed as d [ppm], s for singlet, m for multiplet and b for broad. Mass spectra have been obtained with Varian MAT CH-7 instrument in EPSRC National Centre Swansea, United kindgum, using electron impact ionization (70eV).

**General synthesis of amino-cyclohexenes(3a-d)by using of microwave irradiation:**

All microwave-assisted reactions were performed in a 50 mL reaction vial, aromatic aldehyde (1 mmol), acetylacetone (2mmol) and aminoalcohol (1mmol) in ethanol (30mL) were mixed and then capped. The mixture was irradiated by microwave at 750W and 80°C with frequent interval times every 10 seconds until the reaction completed at the given time in table 1. The reaction mixture was cooled to room temperature. The solid product was filtered, washed with 5mL commercial ethanol, and purified by recrystallization from 95% EtOH. The reaction time and the yields are listed in Table 1 (Rf =0.80). The euleuant is isopropanol:heptan 3:1

967
General synthesis of amino-cyclohexenes 3a-d by conventional heat:
A solution of 0.02 mole of acetylacetone was added to a mixture of 0.01 mole of the appropriate amino alcohols 1 and 0.01 mole of aromatic aldehyde 2 in 50 ml ethanol. The reaction mixture was refluxed for 3 hours at 80°C and left to cool down at room temperature. A precipitate was obtained, filtered and washed with cold ethanol. The solid products were crystallized from ethanol to afford the formation of 5-N-(2-hydroxyalkyl) amino-2,4-diacyetyl-2,4-diacyetyl-1-methyl-3-aryl-4-cyclohexen-1-ol compounds 3a-d.

Table 1 represents the comparison between the yield and the time consumed in synthesis of cyclohexenes 3a-d derived from amino alcohols by using of microwave irradiation and conventional heat.

<table>
<thead>
<tr>
<th>compound</th>
<th>Microwave irradiation at 80°C</th>
<th>Conventional heat at 80°C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (min)</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>3a</td>
<td>8</td>
<td>92</td>
</tr>
<tr>
<td>3b</td>
<td>10</td>
<td>72</td>
</tr>
<tr>
<td>3c</td>
<td>5</td>
<td>90</td>
</tr>
<tr>
<td>3d</td>
<td>5</td>
<td>84</td>
</tr>
</tbody>
</table>

5-N-(2-Hydroxypropyl)amino-2,4-diacyetyl-1-methyl-3-phenyl-4-cyclohexen-1-ol (3a): This compound was obtained as colourless crystals (92%, ethanol, m.p. 179°C). IR spectrum, cm–1: 1590 (C=C), 1703 (C=O), 3100–3200 (OH), 3300–3400 (NH). ppm (DMSO-d6 or CD3COCD3) (signals assignment was based on NOESY and DEPT spectra): 1.19 s (6H, 2Me [chain Me & C1-Me]), 1.53 s (3H, Me of C2-Ac), 1.90 s (3H, Me of C4-Ac), 2.52 s (2H, CH2 chain), 3.6 d (2H, C6 cyc), 3.6 s (1H, OH [of aminoalcohol]), 3.8 t (1H, CH chain), 4.1 d (1H, C3 cyc), 4.4 s (1H, OH at C1), 4.8 d (1H, C2 cyc), 7.0-7.4(m, 5H, Ar), 11.5 (s,1H, NH). 13C-NMR spectrum, ppm (DMSO-d6): 10 (1-CH3 (alcoholic), 28 (Me at C1), 29 (2CH3 Ac), 41(CH2 chain), 50 (1CH2 [C6cyc]), 61 (2CH cyc), 97(C1 cyc), 105 (C5 cyc) 125-130 (5CH- Ar), 148 (C3, cyc), 160 (C2, C4 cyc), 195, 206 (2CO).

5-N-(2-Hydroxyethyl)amino-2,4-diacyetyl-1-methyl-3-(4-chlorophenyl)-4-cyclohexen-1-ol (3b): (72%, ethanol, m.p. 151°C); IR spectrum, cm-1: 1600 (C=C), 1720 (C=O), 3100–3200 (OH), 3300–3400 (NH). 1H-NMR, ppm, (DMSO-d6 or CD3COCD3) (signals assignment was based on NOESY and DEPT spectra): 1.19 s (6H, 2-CH3 [chain and C1]), 1.53 s (3H, C4-Ac), 1.90 s (3H, C2-Ac), 2.52 s (2H, CH2 chain), 3.6 d (2H, CH2 cyc), 3.6 s (1H, OH cyc), 3.8 t (1H CH chain), 4.1 d (1H, CH at C3), 4.4 s (1H, OH of aminoalcohol), 4.8 d (1H, CH at C2) 7.0-7.4(m, 4H, Ar),11.5 (s,1H, NH). 13C-NMR spectrum, d, ppm (DMSO-d6 ): 10 (1-CH3 (alcoholic), 28 (Me at C1), 29 (2CH3 Ac), 41(CH2 chain), 50 (1CH2 [C6cyc]), 61 (2CH cyc), 97(C1 cyc), 105 (C5 cyc) 125-130 (4CH Ar), 148 (2C aromatic), 195, 206 (2CO).

5-N-(2-Hydroxyethyl)amino-2,4-diacyetyl-1-methyl-3-phenyl-4-cyclohexen-1-ol (3c): IR spectrum, cm-1: 1589 (C=C), 1703 (C=O), 3100–3200 (OH), 3300–3400 (NH). 1H-NMR, ppm (DMSO-d6 or CD3COCD3, signals assignment was based on NOESY and DEPT spectra): 1.10 s (3H, Me at C1), 1.53 s (3H, Me of C4-Ac), 1.95 s (3H, Me of C2-Ac), 2.55 s (2H, CH2 cyc), 3.6 d (4H, 2CH2 chain ), 3.6 s (1H, OH cyclic), 4.18 d (1H, CH cyc), 4.5 s (1H, OH aminoalcohol), 4.8 t (1H, CH cyc), 7.0-7.4(m, 5H, Ar), 11.5 (s,1H, NH). 13C-NMR spectrum, ppm (DMSO-d6 ) : 18 (1-CH3 at C1), 20 (CH3 at C4), 23 (CH3 at C2), 41, 43 (2CH2 chain), 42 (1CH at C3 cyc), 60 (1CH2 cyclic), 61 (2CH2 cyclic), 64(C1 cyc), 103 (C5 cyc), 125-130 (4CH Ar), 148 (2C aromatic), 195, 206 (2CO).

5-N-(5-Hydroxypentyl)amino-2,4-diacyetyl-1-methyl-3-(4-chlorophenyl)-4-cyclohexen-1-ol (3d): (84%, ethanol, m.p. 168°C); IR, cm-1: 1589 (C=C), 1703 (C=O), 3100–3200 (OH), 3300–3400 (NH). 1H-NMR, ppm (DMSO-d6 or CD3COCD3, signals assignment was based on NOESY and DEPT spectra): 1.20 s (3H, 1-Me), 1.50 m (8H, 4CH2 chain), 1.85 s (3H, C2-Ac), 2.1 s (3H, C4- Ac), 2.8 s (1H, OH at C1cyc), 3.18 t (2H, CH2-O chain), 3.5 s (2H CH2 cyclic), 3.7 d (1H, CH cyc), 4.3 s (1H, OH aminoalcohol), 7.1-7.4(m, 4H, Ar), 11.7 (s,1H, NH). 13C-NMR spectrum, ppm (DMSO-d6 ): 10 (1- Me at C1cyc), 18-19 (3CH2 chain), 42 (Me of Ac at C4), 43 (2H, 1CH2 cyclic), 44 (Me of Ac at C2), 61 (CH2-N, chain), 64 (CH2-O, chain), 68 (C4=C5, cyc), 93 (C-Cl), 103 (C5-N, cyc), 128-130 (CH Ar), 206, 208 (2CO group).
RESULTS AND DISCUSSION

The microwave irradiation of a mixture of acetylacetone, primary amino alcohols 1a-c and aromatic aldehydes 2a,b revealed the formation of 5-N-(2-Hydroxypropyl)amino-2,4-diacetyl-1-methyl-3-phenyl-4-cyclohexen-1-ol 3a, 5-N-(2-Hydroxyethyl)amino-2,4-diacetyl-1-methyl-3-(4-chlorophenyl)-4-cyclohexen-1-ol 3b, 5-N-(2-Hydroxyethyl) amino-2,4-diacetyl-1-methyl-3-phenyl-4-cyclohexen-1-ol 3c, and 5-N-(5-Hydroxypentyl)amino-2,4-diacetyl-1- methyl-3-(4-chlorophenyl)-4-cyclohexen-1-ol 3d respectively. The reaction mechanism is based on Aldol-Knoevenagel condensation and Michael addition process. The amino alcohols 1 in this reaction are acting as a Lewis base reagent and as reactant in the same time. So, elimination of a hydrogen proton from the active methylene center in acetylacetone is leading to generate the carbanion 5 which in turn is attacking the carbonyl group of the aldehydes 2 to form the alcohol 7 via the intermediate 6. Elimination of water from 6 is affording the arylenes 7 which...
undergo Michael addition of the carbanion 5 to give the tetraone 8. An intra Aldol-condensation of 8 catalysed by aminoaolcohols 1 is leading ultimately to the formation of cyclohexanones 11 via the intermediates 9 and 10. The condensation reaction of cyclohexanone 11 with the aminoaolcohols is producing the imin compound 2 which tutomerised into the final product of amino cyclohexene derivatives 3a-d (Scheme 2).

CONCLUSION

In this work we have reported one of fast and friendly environmentally preparation method of amino cyclohexene derivatives in a very good yield by the assistance of microwave irradiation of three simple component compounds in one step as part of our economic and green chemistry protocol.

Acknowledgment

The authors are grateful to the higher education authorities in both of Republic of Azerbaijan and Arab Republic of Egypt for their moral and financial support. We are also deeply thanked Baku State University for facilitating this study.

REFERENCES

[10] M Barbenni; P Guarda; M Villa; P Cabeila; F Pivetti and F Ciaccio, Flavour Fragrance J., 2000, 5, 27.
[14] H Plach; E Bartmann; E Poetsch; S Naemura and B Rieger, SJD Digest, 1992, 13.
[34] JA Varela; C Gonzalez-Rodriguez; SG Rubín; L Castedo and S Carlos, J. Am. Chem. Soc., 2006, 128, 9576.
[37] Mohamed, S. K. et al PhD research study; Sohag Uni., Egypt, under process.
[38] EN Garibov; IA Rzaeva; NG Shykhaliev; AI Kuliev; VM Farzaliev and MA Allakhverdiev, *Russian J. of Applied Chem.*, 2010, 83 (4), 707.